

## II. REMARKS

Claims 1-27 are pending in the application. Claims 8-18 and 20-25 are withdrawn. By this Amendment, claims 1 and 24 are amended. The amendments are supported by the originally filed specification and claims. In particular, the amendments to claim 1 are supported, for example, by page 3, lines 14-21 of the specification. Meanwhile, claim 24 is amended to correct a typographical error. No new matter is added.

Claims 1-7, 19, and 26-27 are rejected under 35 U.S.C. § 112, first paragraph, for insufficient written description. This rejection is traversed.

Applicants submit that "Newcastle disease virus Z" is sufficiently described by the specification and originally filed claims. For example, originally filed claim 1 discloses that "Newcastle disease virus Z has at least two of the features selected from the group consisting of (1) a F<sub>0</sub> protein cleavage site having at least two less basic amino acid residues than a F<sub>0</sub> protein cleavage site of Newcastle disease virus wild type strain Beaudette C; (2) an amino acid having a non-aromatic side chain at the N terminus of the F<sub>1</sub> cleavage fragment, wherein the amino acid having a nonaromatic side chain is glycine, alanine, valine, leucine or isoleucine; and (3) an open reading frame of a HN glycoprotein being longer than an open reading frame of a HN glycoprotein of Newcastle disease virus wild type strain Beaudette C."

As described in the present specification, Applicants had possession of the system to manipulate the genome of Newcastle disease virus (NDV) at the time of the original filing of this application. Newcastle disease virus Z could be engineered from a

strain of NDV with the modifications clearly described in claims 1-7, 19, and/or 26-27 and these modifications were achieved in Applicants' laboratory. The characteristic of Newcastle disease virus Z is attenuated like other live attenuated NDV vaccines.

Further, this application discloses creative engineering of a recombinant live attenuated NDV vaccine that will be more genetically stable than currently-available natural vaccine strains. For example, the specification notes that "the ability to directly engineer mutations into cDNA would make it possible to generate defined attenuated strains where cDNA would serve as a stable vaccine 'seed'" (specification, page 3, lines 15-17). Applicants expect that the genetic stability of NDV Z will be great; however, this feature can only be determined after it has been used in the field for many years. Therefore, Applicants submit that it would have been impossible to know all of the characteristics of NDV Z at the time of the application. This does not render Applicants' description indefinite, however.

As previously noted by the Examiner, "[i]t is well settled that the claimed subject matter need not be supported by an explicit, word for word recitation, but something more than a suggestion is needed to satisfy the requirement for an adequate written description" (March 18, 2005 Office Action, page 4, lines 14-16). Applicants submit that "an explicit, word for word recitation" is present, as the claims are original and are adequately supported by the specification.

Under MPEP § 2163.03 a written description issue "can arise in a number of different circumstances where it must be determined whether the subject matter of a claim is supported in an application as filed." However, MPEP § 2163.03 notes that

"[w]hile a question as to whether a specification provides an adequate written description may arise in the context of an original claim which is not described sufficiently ..., there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. ... Consequently, rejection of an original claim for lack of written description should be rare" (emphasis added). Further, MPEP § 2163.03 states that the written description requirement will "typically" arise in the following circumstances:

- (1) amendment affecting a claim;
- (2) reliance on filing date of parent application under 35 U.S.C. § 120;
- (3) reliance on priority under 35 U.S.C. § 119; or
- (4) support for a claim corresponding to a count in an interference.

Circumstance (1) does not apply at the present time, as claims 1-7, 19 and 26-27 are originally filed claims. Applicants respectfully submit that circumstances (2) and (3) are not applicable, as the provisional applications provide adequate written support for the presently claimed invention (please see Applicants' remarks in the Response filed June 17, 2005). Meanwhile, circumstance (4) does not apply at the present time, as no interference is known at this time. As claims 1-7, 19 and 26-27 are originally filed claims, Applicants respectfully submit that a written description rejection is not appropriate. Further, Applicants note that the "examiner has the initial burden of presenting by a preponderance of the evidence why a person skilled in the art would not recognize in an applicant's disclosure a [written] description of the invention defined by the claims."

Thus, for at least the above reasons, Applicants submit that the originally filed specification and claims provide sufficient written description for Newcastle disease virus Z. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-7, 19 and 26-27 under 35 U.S.C. § 112, first paragraph.

Claims 1-3, 5, 15, and 19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Millar et al. (Journal of General Virology (1998) 69: 613-620). This rejection is traversed.

Present claim 1 discloses “[a] vaccine for Newcastle disease comprising a genetically engineered live attenuated Newcastle disease virus Z, wherein the Newcastle disease virus has at least two of the features selected from the group consisting of (1) a F<sub>0</sub> protein cleavage site having at least two less basic amino acid residues than a F<sub>0</sub> protein cleavage site of Newcastle disease virus wild type strain Beaudette C; (2) an amino acid having a non-aromatic side chain at the N terminus of the F<sub>1</sub> cleavage fragment, wherein the amino acid having a nonaromatic side chain is glycine, alanine, valine, leucine or isoleucine; and (3) an open reading frame of a HN glycoprotein being longer than an open reading frame of a HN glycoprotein of Newcastle disease virus wild type strain Beaudette C” (emphasis added).

Millar et.al. does not teach or suggest a “genetically engineered live attenuated Newcastle disease virus Z” of claim 1, much less a vaccine thereof. In contrast, Millar et al. merely determined the “nucleotide sequences of the fusion (F) and haemagglutinin-neuraminidase (HN) glycoprotein genes of the extremely avirulent Newcastle disease virus (NDV) strain Ulster” and compared the “two glycoprotein

sequences with those of more virulent NDV strains” to suggest “an explanation for the molecular basis of the wide-ranging differences in virulence observed between strains of NDV” (Millar et al., Abstract). While Millar et al. discloses the following:

The open reading frame corresponding to the Ulster HN glycoprotein extended beyond the C terminus of more virulent strains. This C-terminal extension was assumed to be responsible for the origin of the HN precursor (HN<sub>0</sub>) found in strain Ulster and other extremely avirulent strains of NDV. There were fewer basic amino acids at the cleavage site of F<sub>0</sub> in strain Ulster than are present in more virulent strains, which may be responsible for the absence of cleavage and activation of F<sub>0</sub> from this strain in many host cells. In more virulent strains of NDV ... a phenylalanine residue occurs at the N terminus of the F<sub>1</sub> cleavage fragment. The occurrence of a leucine residue at this position in strain Ulster may be partly responsible for the lack of virulence of this strain.

(Millar et al., Abstract) (emphasis added), the roles of F and HN genes in virulence have only recently been determined. See, e.g., Panda et al., Microb. Pathog. (2004) 36: 1-10; or Huang et al., J. Virol. (2004) 78: 4176-84. These papers did not teach or suggest a vaccine with NDV engineered with such changes.

For at least the above reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-3, 5, 15, and 19 under 35 U.S.C. § 102(b) as being anticipated by Millar et al.

Claims 1-3, 5, 15, and 19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Stone (Avian Diseases (1989) 33: 157-162). This rejection is traversed.

Stone discloses preparation of an inactivated vaccine from NDV strains La Sota and Ulster. In contrast, claim 1 discloses “genetically engineered live attenuated Newcastle disease virus Z” (emphasis added). Inactivated vaccines can be prepared with any NDV strain, as modification of the F and/or HN gene is not necessary. As

such, Stone does not teach or suggest the NDV strain of the present invention, much less a vaccine thereof.

For at least the above reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-3, 5, 15, and 19 under 35 U.S.C. § 102(b) as being anticipated by Stone.

Claims 4 and 6-7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over by Millar et al. (Journal of General Virology (1998) 69: 613-620) in view of Peeters et al. (WO 99/66045). This rejection is traversed.

Applicants submit that dependent claims 4 and 6-7 are patentable for at least the same reasons as claim 1.

Further, Applicants agree with the Examiner that “[c]laims 4, and 6-7 differ from Millar in that Millar does not teach the specific codons recited in these claims” (Office Action, page 5). However, Applicants respectfully submit that Peeters et al. does not satisfy the deficiencies of Millar et al.

Peeters et.al. does not teach or suggest a specific attenuating mutation that will be used to attenuate NDV (see, e.g., the “genetically engineered live attenuated Newcastle disease virus Z” of claim 1 (emphasis added)). Attenuation can be achieved by many different types of mutations introduced in any gene or non-coding sequence. It is challenging and creative to determine the specific type of attenuating mutation, the exact site and the gene in which it will be introduced. Therefore, Applicants respectfully submit that present claims 4 and 6-7 would not have been obvious to those of skill in the art in view of Millar et al. and Peeters et al.

For at least the above reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 4 and 6-7 under 35 U.S.C. § 103(a) as being anticipated by Millar et al. in view of Peeters et al.

Claims 26-27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over by Millar et al. (Journal of General Virology (1998) 69: 613-620) and Peeters et al. (WO 99/66045) as applied to claims 4 and 6-7 above, and further in view of Schijns et al. (Vaccine (2000) 18: 2147-2154). This rejection is traversed.

Applicants respectfully submit that claims 26-27 properly claim priority from U.S. Provisional Application Nos. 60/132,597 and 60/171,072.

As noted in the previously filed response filed June 17, 2005, independent claims 1 and dependent claims 26-27 are supported by the provisional applications upon which priority is claimed as follows :

For example, U.S. Patent Provisional Application No. 60/171,072 ("the '072 provisional") states the following:

Sequence analysis of several avirulent strains [of Newcastle disease virus (NDV)] have suggested that attenuation in NDV occurs by three different mechanisms: (1) avirulent strains have few basic residues (x-Arg/lys-x-x-Arg) at the F0 protein cleavage site, where as virulent strains have multibasic residues (Arg-Arg-x-Arg/lys-Arg) at the F0 protein cleavage site, (2) in some avirulent strains the open reading frame of the HN glycoprotein extends beyond the C terminus of more virulent strains and this terminal extension was assumed to be responsible for the origin of the HN precursor (HN0) found in avirulent strains, and (3) in some avirulent strains a leucine residue is present at the N terminus of the F1 cleavage fragment in place of a phenylalanine residue at this position in virulent strains.

('072 provisional, page 1, lines 9-17);

We propose to engineer attenuated NDV vaccine strains by combining all three mechanisms of attenuation.

('072 provisional, page 2, first paragraph);

We propose to recover NDV with amino acid changes at the cleavage site. The codon of the changed amino acid changes at the cleavage site. The codon of the changed amino acid will be different from that of the original amino acid by at least two nucleotides; therefore, will stabilize reversion to a basic residue.

('072 provisional, page 2, second paragraph);

The above changes will not only be done in our existing full-length cDNA clone of NDV Strain Beaudette C.

('072 provisional, page 2, lines 9-10); and

In our proposed recombinant NDV strains the codes of the amino acids in the cleavage site will be changed so that they will contain the same amino acids as other avirulent strains but will require reversion of five or six nucleotides. ... Furthermore, our NDV vaccines will also contain the other two mechanisms of attenuation, presence of Leucine in +1 position and cleavable HN protein.

('072 provisional, paragraph bridging pages 5-6).

Meanwhile, U.S. Provisional Patent Application No. 60/132,597 ("the '597 provisional") discloses a complete map of the genome of Newcastle disease virus (NDV) strain Beaudette C depicted by Figure 3 and described on page 7 ("the genome of NDV strain Beaudette C is 15,186 nucleotides").

In particular, claims 26-27 are supported by page 5, last line of the '072 provisional ("[a] genetically engineered NDV carrying cytokine genes") and page 2, last sentence and page 8, lines 21-22 (and page 8, last line) of the '597 provisional ("the genes for cytokines can be inserted into the NDV genome for coexpression").

(June 17, 2006 Amendment) (emphasis added). Further, the '597 provisional discloses that NDV "causes a highly contagious and fatal disease affecting all species of birds"



and “[t]he most commonly used method of vaccination has been the exposure of chickens ...” (‘597 provisional, page 1, first paragraph). According, Applicants submit that there is sufficient written support for avian cytokines. Further, an interleukins are well known cytokines to those of skill in the art. Please see the attached web pages.

Accordingly, Applicants submit that there is sufficient support for claims 1, and 26-27. As such, Schijns et al. is improperly cited against the present application.

Regardless, Applicants respectfully submit that dependent claims 26-27 are patentable for at least the same reasons as independent claim 1.

Further, Applicants respectfully submit that Schijns et al. does not satisfy the deficiencies of Millar et al. and Peeters et al. Please see the above discussion distinguishing Millar et al. and Peeters et al. In addition, Applicants agree with the Examiner that “Millar does not teach a vaccine for NDV that carries at least one gene encoding an avian cytokine wherein said cytokine is an interleukin” (Office Action, page 5). Further, Peeters et.al. does not teach or suggest avian cytokines, much less interleukin avian cytokines. In contrast, Peeters et al. discloses “genes encoding human interferons, chemokines or other immune stimulatory proteins” that do not include avian cytokines (see, e.g., Peeters et al., paragraph bridging pages 22-23) (emphasis added).

Meanwhile, Schijns et al. observed the immunoadjuvant activities of chicken interferons with tetanus toxoid as the bacterial model antigen. However, Schijns et al. disclosed that tetanus toxoid could be used only for certain types of vaccines. For example, Schijns et al. did not observe “improvement of antibody responses with

infectious bursal disease virus (Schijns et al., Abstract). Further, Schijns et al. did not teach or suggest the use of NDV as an antigen in their study, nor the use of chicken cytokines (e.g. chicken interleukin-1 $\beta$ ) for NDV. Schijns et al. merely discloses that "Karaca and co-workers .. have demonstrated that vaccination of embryonated chicken eggs or newly hatched chickens with a fowlpox virus co-expressing chicken type I IFN ... together with Newcastle disease virus (NDV) HN and F genes, results in impaired antibody response against NDV in young chickens" (Schijns et al., page 2148, first full paragraph of the left column) (emphasis added). As such, Applicants submit that Schijns et al. does not teach or suggest "Newcastle disease virus Z [that] carries at least one gene encoding an avian cytokine" (claim 26), much less where the "said cytokine is an interleukin" (claim 27).

For at least the above reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 26-27 under 35 U.S.C. § 103(a) as being anticipated by Millar et al. in view of Peeters et al. as applied to claims 4 and 6-7, and further in view of Schijns et al.

### III. Conclusion

Applicants respectfully submit that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

In the event that this paper is not considered to be timely filed, an appropriate extension of time is requested. Any fees for such an extension, together with any additional fees that may be due with respect to this paper, may be charged to counsel's Deposit Account Number 01-2300, referencing Docket Number 108172-00070.

Respectfully submitted,

  
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Enclosures: Petition for Extension of Time (3 months)  
Web pages

# Interleukin

From Wikipedia, the free encyclopedia

**Interleukins** are a group of cytokines that were first seen to be expressed by white blood cells (leukocytes, hence the *-leukin*) as a means of communication (*inter-*). The name is sort of a relic though; it has since been found that interleukins are produced by a wide variety of bodily cells. The function of the immune system depends in a large part on *interleukins*, and rare deficiencies of a number of them have been described, all featuring autoimmune diseases or immune deficiency. interleukins are part of the immune system.

A list of *interleukins* with function:

- IL-1: secreted by macrophages, induces acute phase reaction
- IL-2: secreted by T cells, stimulates growth and differentiation of T cell response. Can be used in immunotherapy to treat cancer.
- IL-3: secreted by T cells, stimulates bone marrow stem cells.
- IL-4: involved in proliferation of B cells, and the development of T cells and mast cells. Important role in allergic responses.
- IL-5: role in stimulation of B cells, eosinophil production, IgA production
- IL-6: secreted by macrophages, induces acute phase reaction
- IL-7: involved in B, T and NK cell survival, development and homeostasis
- IL-8: Neutrophil chemotaxis
- IL-9: stimulates mast cells
- IL-10: inhibits Th1 cytokine production
- IL-11: acute phase protein production
- IL-12: NK cell stimulation, Th1 cells induction
- IL-13: Stimulates growth and differentiation of B-Cells, inhibits Th1 cells and the production of macrophage inflammatory cytokines
- IL-17: Induces production of inflammatory cytokines
- IL-18: Induces production of Interferon-Gamma (IFN $\gamma$ )

## Interleukins

IL-1 | IL-2 | IL-3 | IL-4 | IL-5 | IL-6 | IL-7 | IL-8 | IL-9 | IL-10 | IL-11 | Induces Treg Function IL-12 | IL-13 | IL-14 | IL-15 | IL-16 | IL-17 | IL-18 | IL-19 | IL-20 | IL-21 | IL-22 | IL-23 | IL-24 | IL-25

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# Cytokine

From Wikipedia, the free encyclopedia

**Cytokines** are soluble proteinaceous substances produced by a wide variety of haemopoietic and non-haemopoietic cell types, and are critical to the functioning of both innate and adaptive immune responses. Apart from their role in the development and functioning of the immune system, and their aberrant modes of secretion in a variety of immunological, inflammatory and infectious diseases, cytokines are also involved in several developmental processes during human embryogenesis.

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## Effects

Each cytokine binds to a specific cell-surface receptor. Subsequent intracellular signalling cascades then alter cell functions. This may include the upregulation and/or downregulation of several genes and their transcription factors, that result in production of other cytokines, or increase in the number of surface receptors for other molecules, or suppress their own effect by feedback inhibition.

Therefore, cytokines are characterised by considerable **redundancy**, in that many cytokines can share similar functions. In a similar manner, cytokines are also **pleiotropic** (acting on many different cell types). Of course, this would be an anticipated corollary if one considers the simple fact that a given cell type may express receptors for more than one cytokine, or that many different tissues can express receptors for the same cytokine.

Generalisation of functions is not possible with cytokines; nonetheless, their actions may be comfortably grouped as:

- **autocrine**, if the cytokine acts on the cell that secretes it
- **paracrine**, if the action is restricted to the immediate vicinity of a cytokine's secretion
- **endocrine**, if the cytokine diffuses to distant regions of the body (carried by blood or plasma) to affect different tissues.

Cytokines binding to antibodies paradoxically have a stronger immune effect than the cytokine alone. This may lead to lower therapeutic doses and perhaps fewer side effects.

## Nomenclature

Cytokines have been variously named as lymphokines, interleukins and chemokines, based on their presumed function, and their cell of secretion or target of action. Because cytokines are characterised by considerable redundancy and pleiotropism, such a distinction, with exceptions, is obsolete.

The term **interleukin** was initially used by researchers for those cytokines whose presumed targets are principally leukocytes. The term **chemokine** referred to a specific class of cytokines that mediated chemoattraction (chemotaxis) between cells. The latter term alone has been retained (see below); interleukins are now used largely for designation of newer cytokine molecules discovered every day, and have little significance attached to their presumed function.

Of note, IL-8 (interleukin-8) is the only chemokine originally named an interleukin.

## Classification

Cytokines have now been classified into four different types based on structural homology, which has been partly able to separate cytokines that do not demonstrate a considerable degree of redundancy.

- **Four  $\alpha$ -helix bundle family**, the three dimensional structures of whose members have four bundles of  $\alpha$ -helices. This family in turn is divided into three sub-families, **the IL-2 subfamily**, **the interferon (INF) subfamily** and **the IL-10 subfamily**. The first of these three subfamilies is the largest, and contains several non-immunological cytokines including erythropoietin(EPO) and thrombopoietin (THPO). Alternatively four helix bundle cytokines can be grouped into *long chain* and *short chain* cytokines.
- **IL-1 family**, which primarily includes IL-1 and IL-18.
- **IL-17 family**, which is yet to be completely characterised. However, it is known that they have a specific effect in promoting proliferation of T-cells that cause cytotoxic effects.
- **Chemokines**

A more clinically and experimentally useful classification divides immunological cytokines into those that promote the proliferation and functioning of helper T-cells type 1 (example, IL-1, INF- $\gamma$  etc.) and helper T-cells type 2 (IL-4, IL-10, IL-13, TGF- $\beta$  etc.), respectively. It is remarkable that the cytokines that belong to one of these sub-sets tend to inhibit the effects of their counterparts - a tendency under intensive study for their possible role in the pathogenesis of autoimmune disorders.

## Cytokine Receptors

In recent years, the cytokine receptors have come to demand the attention of more investigators than cytokines themselves, partly because of their remarkable characteristics, and partly because a deficiency of cytokine receptors have now been directly linked to certain debilitating immunodeficiency states. In this regard, and also because the redundancy and pleomorphism of cytokines are in fact a consequence of their homologous receptors, many authorities are now of the opinion that a classification of cytokine receptors would be more clinically and experimentally useful.

A classification of cytokine receptors based on their three-dimensional structure has therefore been attempted. (It must be noted that such a classification, though seemingly cumbersome, provides with several unique perspectives for attractive pharmacotherapeutic targets.)

- **Immunoglobulin (Ig) superfamily**, which are ubiquitously present throughout several cells and tissues of the vertebrate body, and share structural homology with immunoglobulins (antibodies), cell-adhesion molecules, and even some cytokines. Examples: IL-1 receptor types.
- **Haemopoietic Growth Factor (type 1) family**, whose members have certain conserved motifs in their extracellular amino-acid domain. The IL-2 receptor belongs to this chain, whose  $\gamma$ -chain (common to several other cytokines) deficiency is directly responsible for X-linked form of Severe Combined Immunodeficiency (X-SCID).
- **Interferon (type 2) family**, whose members are receptors for INF  $\beta$  and  $\gamma$ .

- **Tumour Necrosis Factor (TNF) (type 3) family** whose members share a cysteine-rich common extracellular binding domain, and includes several other non-cytokine ligands like CD40, CD27 and CD 30, besides the ligands on which the family is named (TNF).
- **Seven transmembrane helix family**, the ubiquitous receptor type in animal kingdom. All G-protein coupled receptors (for hormones and neurotransmitters) belong to this family. It is important to note that the chemokine receptors, two of which acting as binding proteins for the HIV virus (CXCR 4 and CCR 5), also belong to this family.

## References

- Gallin J, Snyderman R (eds). *Inflammation: Basic Principles and Clinical Correlates*. 3rd edition, Philadelphia, Lippincott William and Wilkins, 1999.
- Janeway CA et al. (eds). *Immunobiology. The immune system in Health and Disease*, 4th edition, New York, Garland, 1999.
- Roitt I et al. (eds.) *Immunology*. 5th edition, London, Mosby, 2002.
- *Science* Vol. 311 No. 5769, pp. 1875 - 1876, 31 March 2006 DOI: 10.1126/science.1126030 (<http://dx.doi.org/10.1126/science.1126030>)

## See also

- Adipokines
- Apoptosis
- Chemokines
- Cytokine secretion assay
- Cytokine storm
- ELISPOT
- Interleukins
- Interferon
- Granulocyte-colony stimulating factor
- Signal transduction
- Tumor necrosis factor

## External links

- Cytokine Tutorial (<http://microvet.arizona.edu/Courses/MIC419/Tutorials/cytokines.html>)
- Cell Interactions: Cytokines ([http://www-immuno.path.cam.ac.uk/~immuno/part1/lec09/lec10\\_99.html](http://www-immuno.path.cam.ac.uk/~immuno/part1/lec09/lec10_99.html))
- Reperfusion Injury in Stroke (<http://www.emedicine.com/neuro/topic602.htm>).
- Cytokines Online Pathfinder Encyclopaedia (<http://www.copewithcytokines.de/>)

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